

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BV-1060 WO	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/SE2004/001508	International filing date (day/month/year) 20.10.2004	Priority date (day/month/year) 20.10.2003
International Patent Classification (IPC) or national classification and IPC See Supplemental Box		
Applicant BIOVITRUM AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
 - a. ☐ (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows:
 - ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
 - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input checked="" type="checkbox"/> | Box No. II | Priority |
| <input checked="" type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

Date of submission of the demand 13.05.2005	Date of completion of this report 22.12.2005
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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Cover sheet

INTERNATIONAL PATENT CLASSIFICATION (IPC):

C07D 471/04 (2006.01)
A61K 31/404 (2006.01)
A61K 31/437 (2006.01)
A61K 31/438 (2006.01)
A61K 31/4439 (2006.01)
A61K 31/496 (2006.01)
A61P 25/00 (2006.01)
A61P 3/04 (2006.01)
A61P 3/10 (2006.01)
C07D 209/08 (2006.01)
C07D 401/12 (2006.01)
C07D 403/04 (2006.01)
C07D 471/20 (2006.01)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE2004/001508

Box No. I Basis of the report

1. With regard to the language, this report is based on:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

- ☒ the international application as originally filed/furnished
- ☐ the description:
- pages _____ as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☐ the claims:
- pages _____ as originally filed/furnished
- pages* _____ as amended (together with any statement) under Article 19
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☐ the drawings:
- pages _____ as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

The priority is considered valid.

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 14 - 16

because:

☒ the said international application, or the said claims Nos. 14 - 16
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1.(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>4,</u>	YES
	Claims	<u>1-3, 5-13, 17-20</u>	NO
Inventive step (IS)	Claims		YES
	Claims	<u>1-13, 17-20</u>	NO
Industrial applicability (IA)	Claims	<u>1-13, 17-20</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are cited in the search report:

D1) WO 0232863 A1
D2) WO 0236562 A2
D3) WO 0241889 A2
D4) WO 02059088 A1
D5) WO 02085853 A2
D6) WO 02085892 A1
D7) WO 02102774 A1
D8) WO 03104193 A1 (publ. 18.12.2003)
D9) WO 03066632 A1
D10) WO 02100822 A1
D11) WO 2004000828 A1 (publ. 31.12.2003)

The claimed invention relates to novel tetrahydrospiro{piperidine-2,7'-pyrrolo[3,2-b]pyridine} derivatives and to novel indole derivatives useful in the treatment of 5-HT₆ receptor-related disorders. Mentioned disorders are obesity, type 2 diabetes and CNS related disorders.

D1-D7 relate to indole derivatives useful in the treatment of 5-HT₆ receptor-related disorders. Mentioned disorders are obesity, type 2 diabetes and CNS related disorders.

The compounds in D1-D7 seem to be included in the scope of the present application when U, W1, W2, W3, Z and Y are carbon, when the binding between U and W1 and between W2 and W3 are

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: BOX V

double-bonds and when P is $-S(O)_2R_1$. Some of the shown substitutions in R4 position in the application and in D1-D7 are the same. The known structure elements in the cited documents are the same as structure elements 1, 8, 9 and 18 mentioned in claim 1 on page 44 and structure elements 1, 3, 6, 8 and 10 mentioned in claim 1 on page 45 (structures 18 and 10 are the same) in the present application. Claims 1-3, 5-13 and 17-20 lack novelty in those parts cited above.

Present claims 1-13 and 17-20 relate to an extremely large number of possible compounds. Support or disclosure within the meaning of PCT Article 6 is to be found, however, for only a very small proportion of the compounds. The claimed provisions are unclear as there is no information in the description about what kinds of compounds are included in the claims. Only a few tetrahydrospiro{piperidine-2,7'-pyrrolo[3,2-b]pyridine} derivatives and indole derivatives are prepared.

From the description, it is clear that only a few compounds concerning 1',4',5',6'-tetrahydrospiro{piperidin-2,7'-pyrrolo[3,2-b]pyridine} derivatives are prepared, when U is carbon, R4 and R4' make a heterocyclic ring and when W1 is nitrogen. These compounds differ from the known in the ring structure.

D2 is considered to be the closest prior art and discloses indole derivatives substituted with a piperazine group in the position for R4. The compounds from D2 are included in the general scope of the application. The claimed compounds differ from the known prepared compound 7 in that P is $NHSO_2Ph$ instead of SO_2Ph .

It is obvious from the application that an $NHSO_2Ph$ group is on an equality with an SO_2Ph group.

In the light of the prior art and having regarded the present description and claims, the problem underlying the present application is to find further compounds having affinity for the 5-HT₆ receptor.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: BOX V

The solution proposed in claims 1-13 and 17-20 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

From the description, it is known that all the compounds which are included in the application have the same therapeutical use and the compounds are in the same category.

It is common practice to synthesise analogues of known compounds. In the present case, D1-D7 as well as this application, may serve as examples.

The selected novel compounds must show an unexpected and advantageous effect over the prior art. No such effect has been demonstrated for the present compounds. In the absence of relevant /biological/activity data to the support of the compounds, no inventive step can be acknowledged for the entire scope of the claims. The basis for recognition of inventive step of the present compounds over the closest prior art might lie in the assessment that, particularly in the realm of biologically active compounds, even small structural modifications may cause dramatic changes in activity.

However, the structural differences between the compounds of the prior art D1-D7 and the present compounds are at least as great as the structural difference between the latter compounds and the present, structurally more remote compounds. Thus, claims 1-13 and 17-20 lack inventive step.

D9 and D10 disclose the general state of the art and are not considered to be particular relevant.

Documents D8 and D10 were published after the claimed priority date, on presumption that the priority is valid, this document is not considered as prior art.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Present claims 1-13 and 17-20 relate to an extremely large number of possible compounds. Support or disclosure within the meaning of PCT Article 6 is to be found, however, for only a very small proportion of the compounds. The claimed provisions are unclear as there is no information in the description about what kinds of compounds are included in the claims. Besides, no compounds are prepared from that part of the claims. Only a few tetrahydrospiro{piperidine-2,7'-pyrrolo[3,2-b]pyridine} derivatives and indole derivatives are prepared.